

FGF23 and Malnutrition in Maintenance Hemodialysis Patients: A Single-Center Study

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Abstract

Background: Malnutrition is a prevalent complication in patients on maintenance hemodialysis and is considered a major risk factor for mortality in those patients. FGF23 has also been associated with mortality in dialysis patients. Little is known about the association between FGF23 and malnutrition in such patients.

Aim of the study: The aim of this study was to investigate possible relationship between FGF23 and malnutrition in maintenance hemodialysis patients. 85 patients on maintenance hemodialysis were studied. In addition to routine laboratory parameters, serum intact fibroblast growth factor-23 levels were done, and anthropometric measures were done after reaching dry weight which included MAC, WC and WHR. BMI was calculated for all patients. SGA-DMS (Subjective Global Assessment -Dialysis Malnutrition Score) was calculated based on medical history and clinical examination.

Results: The mean BMI was 20.2 ± 3 kg/m². The mean hemoglobin level was 9.7 ± 2 g/dl. The mean serum calcium level was 7.6 ± 1 mg/dl. The mean serum albumin was 3.9 ± 1 g/dl. The mean mid-arm circumference was 22.9 ± 2 cm. The mean waist circumference was 90.5 ± 11 cm. The mean malnutrition score was 28.2 ± 3 points. FGF23 levels ranged from 13.5 to 675 ng/L, and accordingly patients were divided into four quartiles. Patients in the lowest FGF23 quartile showed the shortest dialysis vintage, lowest serum calcium, phosphorus, creatinine, albumin, total proteins, MAC, and the highest iPTH level. The highest malnutrition score was associated with the lowest FGF23 quartile. There was highly significant positive correlation between FGF23 level and each of BMI, WHR ($p=0.006$ and 0.001 respectively) and a highly significant negative correlation with malnutrition score ($p=0.000$).

Conclusion: Low FGF23 levels may be associated with malnutrition in maintenance hemodialysis patients. FGF23 used in conjunction with other objective nutritional assessment tools may be of value in determining nutritional status of hemodialysis patients.

Keywords Fibroblast growth factor-23; Malnutrition; Hemodialysis

Abbreviations BMI: Body Mass Index; FGF23: Fibroblast Growth Factor 23; MAC: Mid Arm Circumference; PTH: Parathyroid Hormone; SGA-DMS: Subjective Global Assessment-Dialysis Malnutrition Score; WC: Waist Circumference; WHR: Waist to Hip Ratio

Introduction

Bone-derived fibroblast growth factor23 (FGF23) is a phosphaturic hormone that has recently emerged as a key regulator in the body's complex axis of mineral metabolism [1]. Several epidemiological studies have observed the relationship between declining kidney function and rising FGF23 concentrations [2,3]. In addition, increased circulating FGF23 appears to portend adverse outcomes in patients with CKD3, [4-6]. As a harbinger of poor outcomes, FGF23 joins an already robust group of established metabolic risk factors afflicting patients with end-stage renal disease (ESRD). Much of the focus on FGF23 has attempted to establish a link between the hormone and maladaptive changes in phosphate homeostasis. However, recent

investigators have attempted to shed light on novel associations between FGF23 and factors unrelated to mineral metabolism [7]. Phylogenic and sequence analyses have shown that FGF23 shares common structural and biological features with FGF19 and FGF21, which are members of the FGF19 subfamily [8]. The FGF19 subfamily has emerged as a set of novel factors that regulate diverse metabolic processes [9]. Importantly, both FGF19 and FGF21 have been implied in the regulation of lipid and glucose metabolism [10-14]. Protein-energy malnutrition is a common complication of hemodialysis and a major risk factor for mortality in patients on maintenance hemodialysis [15,16]. Mild to moderate malnutrition occurs in about one third of maintenance dialysis patients and severe malnutrition occurs in approximately 6% to 8% of those patients [17]. The reliable assessment of nutritional status requires multidisciplinary procedures, including anthropometric measurements, body composition measurements, biochemical measurements, functional assessments, dietary assessments, and subjective assessments [17,18]. Subjective global assessment-Dialysis malnutrition score (SGA-DMS) is a fully quantitative reproducible instrument for assessing the nutritional status of dialysis patients [19,20]. The aims of the present study were (1) to describe the demographic, clinical, and nutritional

characteristics in a cohort of ESRD patients who were on maintenance hemodialysis program in our unit, (2) to test, whether FGF23 associates with malnutrition in maintenance hemodialysis patients, and whether it correlates with SGA-DMS and commonly used anthropometric measurements in such patients.

Patients and Methods

The subjects were recruited from maintenance hemodialysis patients at Ain Shams university hospital in the period from January 2016 to June 2016. The study inclusion criteria were ongoing hemodialysis therapy for 6 months and a stable condition without causes of malnutrition other than CKD as hepatic insufficiency, severe acute heart failure, diabetes mellitus, malignancy, pulmonary diseases, active collagen diseases and patients on steroid therapy. 85 consecutive patients (44 males and 41 females) were enrolled in this study. The mean age was 38.5 ± 9.4 years, the median (IQR) for dialysis vintage was 84 (37-177.5) months. Hemodialysis was performed 3 times/week for 4 hours with the use of hollow-fiber dialyzers and a bicarbonate buffered dialysate. Written informed consent was obtained from all participants after informing them about the steps of study and capability to withdraw at any time. The study protocol was approved by the ethics committees of Ain Shams university faculty of medicine. History taking, physical examinations, anthropometric measurements, and blood analyses were performed in the same week for each patient.

All patients were subjected to

Blood analyses

Full blood count, serum creatinine, blood urea nitrogen (BUN), serum sodium, potassium, phosphorus, calcium, serum albumin and total serum proteins were measured by standard laboratory techniques with the use of an automatic analyzer. Serum intact parathyroid hormone was performed using Cobas p480 supplied by Roche molecular diagnostics. Serum intact fibroblast growth factor-23 levels (FGF-23) done using human fibroblast growth factor-23 (FGF-23) ELISA kits supplied by Glory Science Co., Ltd (2400 Veterans Blvd. Suite 16 – 101, Del Rio, TX 78840, USA). Nutritional assessment using edema-free body weight, body mass index (BMI), mid-arm circumference (MAC), waist circumference (WC), waist to hip ratio (WHR), and SGA-DMS. Body mass index (BMI): Measured according to the formula of $[\text{Weight (kg)}/\text{Height (m}^2)]$ in which the weight was measured in (kilogram) using the balanced digital scale for all subject (wearing light clothing). Height was measured (in meter) using a flexible tape with the patient standing without shoes, heels together and the head in the horizontal plane. Mid-arm circumference: Measured with a flexible non stretchable measure tape. The patient was asked to stand with his/her feet together, shoulders relaxed, and arms hanging freely at the sides. The non-access (fistula free) arm was located to avoid the possibility of an inaccurate measurement. The midpoint on the posterior aspect of the upper arm was established between the acromial and olecranon and marked with a pencil. The measuring tape was placed around the upper arm at midpoint and pulled snugly enough to ensure contact with the arm. The measurement was recorded to the nearest centimeter. Normal values of mid upper arm circumference in male (26-29 cm) and in female (26-28.5 cm). Waist circumference (WC) and waist to hip ratio (WHR): The (WC) was taken to the nearest 0.5 cm with a flexible non stretchable tape measure on the horizontal plane at the level midpoint between the lower rib margin and the iliac crest. $\text{WC} \geq 102$ cm for men

and ≥ 88 cm for women were regarded as abnormal. The (WHR) measured by the ratio between waist circumference (WC) to hip circumference (HC) which was taken as the maximal circumference around the buttocks posteriorly and pubic symphysis anterior to the level of a greater trochanter, the ratio of (WHR) was considered abnormal if >1 in male and >0.85 in female. SGA-DMS: is a fully quantitative scoring system consisting of seven features: weight change, dietary intake, gastrointestinal symptoms, functional capacity, co-morbidity, subcutaneous fat and signs of muscle wasting. Each component has a score from 1(normal) to 5 (very severe). Thus the malnutrition score (sum of all seven components) is a number between 7(normal) to 35 (severely malnourished). A lower score denotes normal nutritional status and a higher score is an indicator of the presence of malnutrition elements, that is the higher the SGA-DMS the stronger the tendency towards protein energy malnutrition [19] as described in Figures 1-3.

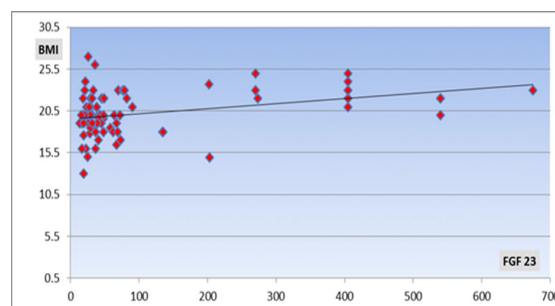


Figure 1: Correlation between BMI and serum FGF-23 levels.

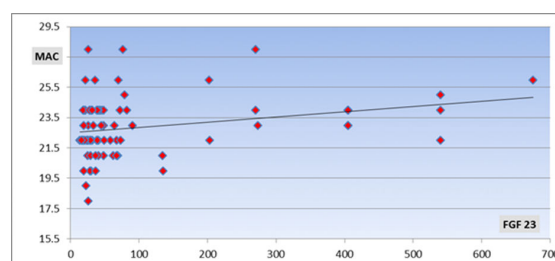


Figure 2: Correlation between MAC and serum FGF23 levels.

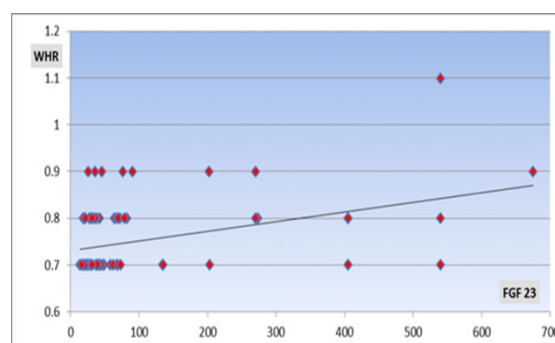


Figure 3: Correlation between WHR and serum FGF23 levels.

Statistical Methods

IBM SPSS statistics V. 22.0 was used for data analysis. Dates were expressed as Mean \pm SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage for categorized data.

Results

All of the subjects (n=85) were Egyptian, there were 44 males (54.1%) and 41 females (45.9%). The mean age was 38.5 ± 9.4 years. The mean BMI was 20.2 ± 3 kg/m². The mean hemoglobin level was 9.7 ± 2 g/dl. The mean serum calcium level was 7.6 ± 1 mg/dl. The mean serum albumin was 3.9 ± 1 g/dl. The mean mid-arm circumference was 22.9 ± 2 cm. The mean waist circumference was 90.5 ± 11 cm. The mean malnutrition score was 28.2 ± 3 points. The

median (IQR) FGF23 levels was 39 (25.5-74.5) ranging from 13.5 ng/L to 675 ng/L. The median (IQR) for dialysis vintage was 84 (37-177.5) ranging from 5 to 300 months. The median (IQR) for body weight was 60 (49.5-71) ranging from 32 to 110 kg. The median (IQR) for phosphorus level was 6 (4.8-7.3) ranging from 2.8 to 9.2 mg/dl. The median (IQR) for PTH was 659 (239.5-1049) ranging from 18.4 to 3461 pg/dl. The median (IQR) for serum creatinine level was 6.3 (4.9-7.8) ranging from 2.1 to 12.9 mg/dl. The median (IQR) for waist to hip ratio was 0.7 (0.7-0.8) ranging from 0.7 to 0.8. FGF23 levels had a wide range value, so for accurate statistical analysis, it was divided into four quartiles.

Tables [1] and [2] show descriptive and comparative analysis of the four FGF23 quartiles for parametric and non-parametric data respectively for all the included patients.

P	F	Q4 (n=21)	Q3 (n=21)	Q2 (n=21)	Q1 (n=22)	FGF-23
		(73.5-657)	(39.5-73)	(25.5-39)	(13.5-25)	(ng/L)
0.241	1.43	36.9 \pm 9	36.7 \pm 10	38.4 \pm 9	41.9 \pm 9	Age (years)
0.527	0.75	132 \pm 39	139 \pm 31	125 \pm 29	137 \pm 30	SBP (mmHg)
0.399	0.99	82.9 \pm 22	88 \pm 19	78.5 \pm 18	85.2 \pm 15	DBP (mmHg)
0.155	1.79	163.5 \pm 18	171.4 \pm 13	173.4 \pm 13	172 \pm 16	Ht (cm)
0.004 **	4.71	21.8 \pm 2	20 \pm 3	19.6 \pm 2	19.3 \pm 2	BMI (kg/m ²)
0.071	2.43	10 \pm 1	10.1 \pm 2	9 \pm 2	9.4 \pm 1	Hb (g/dl)
0.773	0.37	189 \pm 25	187.6 \pm 33	197.4 \pm 35	189 \pm 38	Plt (10 ³ /dl)
0.642	0.56	4.9 \pm 0.7	4.8 \pm 0.8	4.6 \pm 1	4.8 \pm 1	WBCs (10 ³ /dl)
0.728	0.44	7.6 \pm 0.9	7.6 \pm 1	7.7 \pm 1	7.4 \pm 1	Ca (mg/dl)
0.578	0.66	4 \pm 0.4	4 \pm 0.4	3.9 \pm 0.6	3.8 \pm 0.5	Albumin (g/dl)
0.058	0.6	135 \pm 8	141.2 \pm 10	141.5 \pm 8	139 \pm 8	Na (mmol/L)
0.22	3.39	4 \pm 0.7	4.7 \pm 0.8	4.6 \pm 0.8	4.4 \pm 0.5	K (mmol/L)
0.217	1.51	6.9 \pm 1	7.5 \pm 2	7 \pm 0.9	6.7 \pm 0.8	Total Proteins (g/dl)
0.203	1.57	193 \pm 35	205 \pm 41	195 \pm 44	177 \pm 50	Urea-pre(mg/dl)
0.67	0.52	61.7 \pm 13	63 \pm 13	67.1 \pm 19	64 \pm 14	Urea-post (mg/dl)
0.025 *	3.3	23.9 \pm 2	22.8 \pm 1	22.2 \pm 2	22.2 \pm 2	MAC (cm)
0.609	0.61	92.9 \pm 13	89.8 \pm 9	88.4 \pm 11	91 \pm 12	WC (cm)
0.0001 **	24.9	24.8 \pm 4	29 \pm 1	29 \pm 2	29.8 \pm 2	Malnutri-Score (points)

Table 1: Descriptive & comparative analysis of the four FGF23 quartiles in parametric parameters in all hemodialysis patients. Data are shown as mean values with standard deviation (Mean \pm SD) for parametric data. F analysis of variance (ANOVA) for parametric data. P>0.05: Non significant difference *P<0.05: Significant difference ** P<0.01: Highly significant difference.

Patients in the lowest FGF23 quartile showed the shortest dialysis vintage, lowest serum calcium, phosphorus, creatinine, albumin, total proteins, MAC and the highest PTH level. The highest malnutrition score was associated with the lowest FGF23 quartile, whereas the lowest score was associated with the highest FGF23 quartile. Ranke Spearman Correlation test showed a highly significant positive

correlation between FGF23 level and each of BMI, WHR, and a highly significant negative correlation with malnutrition score, also there were a significant positive correlation with each of age and MAC, and a significant negative correlation with Kt/V. There was a non-significant negative correlation with each of Ca, PTH, Na, K, and serum creatinine and a non -significant positive correlation with WC (Table

3). Multi-regression analysis showed that FGF23 was independently associated with age ($p=0.04$), weight ($p=0.001$), height ($p=0.003$), MAC ($p=0.01$), and malnutrition score ($p=0.001$) (Table 4).

Discussion

Malnutrition is highly prevalent in hemodialysis (HD) patients, and it contributes to morbidity and mortality. Fibroblast growth factor-23 (FGF23) and Klotho contribute to chronic kidney disease-mineral and bone disorder (CKD-MBD) in HD patients, but the role that these molecules play in determining nutritional status is currently unknown [21]. The primary finding of this study is that patients in the lowest FGF23 quartile had the lowest serum calcium, phosphorus, creatinine, albumin, total proteins, BMI, and the highest malnutrition score,

which reflected their worse nutritional status compared with the other quartiles. This partially agrees with the results of Mizuiri et al. who reported that among all their studied maintenance hemodialysis patients, the lowest BMI, normalized protein equivalent of nitrogen appearance (nPNA) [22], normalized protein catabolic rate (nPCR) [23], geriatric nutritional risk index (GNRI) [24], serum albumin, creatinine, phosphate, Ca, $\text{Ca} \times \text{P}$ product and iPTH values were seen in the lowest serum FGF-23 quartile ($\text{FGF-23} < 311 \text{ pg/ml}$) [25]. The mean body mass index of our studied population was $20.2 \pm 3 \text{ kg/m}^2$. In fact, HD patients exhibit lower BMIs than age and sex-matched control subjects from the general population [26]. Based on this observation, previous study has shown that increased BMI contributes to survival advantages in dialysis patients [27].

P	H	Q 4 n=21	Q3 (n=21)	Q 2 (n=21)	Q 1 (n=22)	FGF-23 (ng/L)
		73.5- 675	39.5- 73	26- 39	13.5- 25.5	
0.47	2.53	168 (36-222)	90 (37-198)	84 (36-150)	84 (58-147)	Duration (months)
0.21	4.53	1.54 (1.2-1.7)	1.3 (1.1-1.4)	1.1 (0.9-1.5)	1.2 (1-1.5)	KT/V
0.76	1.17	56 (44.5-74)	55.5 (50-68.5)	63 (54.5-70.5)	61 (48-73.2)	Wt (kg)
0.756	1.19	6.7 (4.7-7.6)	6.5 (4.9-7.55)	6.2 (5-7.3)	5.7 (4.2-6.9)	PO4 (mg/dl)
0.289	3.75	427 (179-1037)	643.5 (195-1229)	389 (231-1040)	744 (582-1342)	PTH (pg/dL)
0.128	5.69	5.7 (4.2-7.2)	7.6 (5.4-8.9)	6.9 (5.2-7.5)	5.4 (4.9-8.4)	S-Cr (mg/dl)
0.001**	15.4	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.7-0.8)	0.7 (0.7-0.7)	WHR (cm)

Table 2: Descriptive & comparative analysis of the four FGF-23 quartiles in non-parametric parameters in all hemodialysis patients. Data are shown as median values with 25 and 75% interquartile ranges Median (IQR) for non-parametric data. H (Kruskall Wallis Test) for non-parametric data. $P > 0.05$: Non significant differences* $P < 0.05$: Significant differences ** $P < 0.01$: Highly significant differences.

Significance	p	r	Parameter
S	0.034 *	0.23	Age (years)
NS	0.133	0.164	Duration (month)
S	0.017 *	-0.258	Kt/V
NS	0.803	0.027	SBP (mmHg)
NS	0.543	0.067	DBP (mmHg)
NS	0.626	-0.054	Wt (kg)
NS	0.096	-0.182	Ht (cm)
HS	0.006 **	0.295	BMI (kg/m^2)
NS	0.064	0.202	Hb (g/dl)
NS	0.895	-0.015	Plt (10/dl)
NS	0.617	0.055	WBCs ($10^3/\text{dl}$)
NS	0.295	-0.115	Ca (mg/dl)
NS	0.55	0.066	PO4 (mg/dl)
NS	0.07	-0.197	PTH (pg/dl)
NS	0.54	0.067	Alb (g/dl)

NS	0.279	-0.119	Na (mmol/L)
NS	0.441	-0.085	K (mmol/L)
NS	0.457	0.082	TP (g/dl)
NS	0.683	-0.045	S_creatinine (mg/dl)
S	0.012 *	0.27	MAC (cm)
NS	0.406	0.091	WC (cm)
HS	0.001 **	0.369	WHR (%)
HS	0 **	-0.587	Malnut_Score (points)

Table 3: Correlation between FGF-23 levels values in ng/L and all studied parameters in all hemodialysis patients. Ranked Sperman Correlation Test: FGF23. P>0.05: Non significant correlation. *P<0.05: Significant correlation. **P<0.01: Highly significant correlation.

Parameter	Regression Coefficient	t-value	p-value	Significance	F-Ratio	p	Significance
(constant)	-0.498	-0.166	0.869	NS			
Age	-0.022	-2.091	0.04	S			
Duration	0.002	1.679	0.097	NS			
Weight	-0.064	-3.514	0.001	HS	12.813	0	HS
Height	0.05	3.071	0.003	HS			
MAC	0.198	2.653	0.01	S			
Malnut_Score	-0.275	-6.569	0.0001	HS			

Table 4: Multi-Regression analysis of FGF23 as a dependent variable and the studied parameter that had a significant relation with it. P>0.05: Non significant difference. * P<0.05: Significant difference. ** P<0.01: Highly significant difference.

The obesity paradox [28-31] has created much debate in the renal community regarding the protective effect of obesity in ESRD patients. A recent systematic review [32] of the relationship between BMI and mortality supported the inverse association between BMI and all-cause mortality in adult HD patients, especially in elderly patients. Given that uremic lipid patterns and lower BMI have been linked with increased mortality in patients with advanced kidney disease requiring chronic dialysis [26,33,34] exploration of a potential interrelationship between FGF23 and these risk factors remains an attractive field for research. In a nested case-control sample of 400 patients in the Accelerated Mortality on Renal Replacement (ArMMOR) study, high FGF23 levels were shown to predict 1 year mortality independent of phosphate levels 4. FGF23 levels were also associated with higher mortality in patients with near normal levels of phosphate. A prospective cohort study of 219 dialysis patients undergoing 5-8 h dialysis also demonstrated an association between FGF23 levels and mortality, again independent of phosphate 35. It has been suggested that increased circulating FGF23 levels are independently associated with mortality in incident and prevalent hemodialysis patients [4,35]. However, the median follow-up time in the latter studies was 12 months and 24 months, respectively. Conversely, other studies did not detect any association between circulating FGF23 levels and mortality in hemodialysis patients [36,37]. According to the report by Gutiérrez et al., a combination of increased circulating FGF23 levels and normal or low serum phosphate levels is a significant risk factor for mortality

(P<0.02; odds ratio: 1.8), whereas a combination of high circulating FGF23 levels and high serum phosphate levels (>5.5 mg/dl) is not (P=0.29; odds ratio: 1.1) 4. Another significant finding in this study is the significant positive correlation between FGF23 and nutritional parameters notably BMI, MAC, WHR and malnutrition score, and the significant negative correlation with Kt/V which to our knowledge has not been shown in any studies before. Our study has some limitations. First, due to the cross-sectional study design, a longitudinal causal relationship could not be established between the changes in the plasma FGF23 levels and alterations in malnutrition score and other anthropometric measures. Second, the generalizability of our results is not clear because of the relatively small number of patients in our single-centre study. Larger sample sizes and validation among different cohorts are needed to confirm these results.

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